June 13, 2022

Wayne E. Cascio, MD, FCC
Director
Center for Public Health and Environmental Assessment (CPHEA)
Office of Research and Development (ORD)
Environmental Protection Agency (EPA)
1200 Pennsylvania Ave., NW
Washington, DC 20460

Re: EPA Integrated Risk Information System 2022 Draft Formaldehyde Assessment – Inhalation

Dear Dr. Cascio:

In response to the release of the *Draft Toxicological Review of Formaldehyde – Inhalation* prepared by the U.S. EPA's Integrated Risk Information System (IRIS) program, we respectfully submit the following public comments. Specifically, we address key issues pertaining to the epidemiological literature of lymphohematopoietic malignancies (LHMs) and highlight EPA's dismissal and/or omission of two of our publications that are directly relevant to this topic:.

> Formaldehyde Exposure and Mortality Risks From Acute Myeloid Leukemia and Other Lymphohematopoietic Malignancies in the US National Cancer Institute Cohort Study of Workers in Formaldehyde Industries (2015)(Recipient of the American College of Occupational and Environmental Medicine's Kammer Merit in Authorship Award in 2017)
>
> Peak Exposures in Epidemiologic Studies and Cancer Risks: Considerations for Regulatory Risk Assessment (2019)

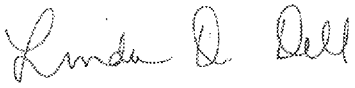
We trust that EPA will find our comments helpful in revising and improving the draft.

Thank you.

Sincerely,

Harvey Checkoway, PhD
Professor, Family Medicine and Public Health
University of California, San Diego

Kenneth A. Mundt, PhD, FACE
Senior Principal Health Scientist
Cardno ChemRisk



Linda Dell, MS
Principal
Ramboll

Comments on U.S. EPA's Integrated Risk Information System (IRIS) Draft Toxicological Review of Formaldehyde – Inhalation

We appreciate the opportunity to provide public comments on the April 2022 IRIS Draft Review of Formaldehyde – Inhalation, but wish to note that we find the 60-day public comment period to be inadequate for responding to a document that is over 800 pages in length (with more than 1000 pages of supplemental material) and not adequately developed or refined. Therefore, we will focus narrowly on EPA's evaluation of the epidemiological literature of lymphohematopoietic malignancies (LHMs) and specifically on EPA's dismissal and/or omission treatment of two of our publications that are directly relevant to this topic:

> Checkoway, H., Dell, L. D., Boffetta, P., Gallagher, A. E., Crawford, L., Lees, P. S., & Mundt, K. A. (2015). Formaldehyde Exposure and Mortality Risks From Acute Myeloid Leukemia and Other Lymphohematopoietic Malignancies in the US National Cancer Institute Cohort Study of Workers in Formaldehyde Industries. Journal of Occupational and Environmental Medicine, 57(7), 785–794. https://doi.org/10.1097/JOM.0000000000000466

> Checkoway, H., Lees, P., Dell, L. D., Gentry, P. R., & Mundt, K. A. (2019). Peak Exposures in Epidemiologic Studies and Cancer Risks: Considerations for Regulatory Risk Assessment. Risk Analysis, 39(7), 1441–1464. https://doi.org/10.1111/risa.13294

The first is a reanalysis of the data analyzed and published by Beane Freeman et al. (2011), a study EPA describes as critical to the Formaldehyde Review. We kindly were provided the data by NCI via a Technology Transfer Agreement and in our publication we not only replicate most of the earlier results, but provide additional analyses including new analyses focusing on acute myeloid leukemia (AML, the subtype of myeloid leukemia that has been associated with other environmental exposures); analyses of absolute peak formaldehyde exposure, a more conventional assessment of elevated exposure excursions; and analyses of absolute peak exposure and AML and chronic myeloid leukemias (CML) (which are discrete malignancies with different etiologies) (Checkoway et al., 2015). We are concerned with the lack of proper characterization of our methods for deriving absolute peak exposures and subsequent dismissal of our study due to an apparent misunderstanding of our analyses and their interpretation.

The second publication was not discussed or cited in the 2022 Draft. This was a review of peak exposure methodology with illustrative examples including formaldehyde (also based on the NCI data) (Checkoway et al., 2019). This publication provides additional information for the EPA to consider in its evaluation of the utility of epidemiological data in dose-response in risk assessment

Major components of the characterization of our analyses of the NCI cohort and their integration into the broader evidence for myeloid leukemia as a whole (and specifically AML, a malignancy previously associated with chemical exposure including benzene) in the 2022 Draft are summarized in the following sections. Copies of both studies (both are Public Access publications) are attached.

The EPA mischaracterized the findings of the reanalysis of the NCI cohort study by Checkoway et al. (2015) and downgraded the exposure assessment without consideration of the issues with the peak exposure definition in the Beane Freeman et al. (2009) analysis of myeloid leukemia (addressed in Checkoway et al. 2019 – see below).

In the 2022 draft IRIS assessment, the EPA states:

> *The Checkoway et al. (2015) reanalysis of Beane Freeman et al. (2009) reported nonsignificant increased risks of AML and CML after redefining the referent group to include all workers with peak exposures of less than 2 ppm as well as some originally classified as having peak exposures of greater than 4 ppm because those worker's peak exposures were thought to be either too frequent or too rare (Beane Freeman et al., 2009). The result of this change in exposure assessment shifted nine cases of myeloid leukemia from the highest exposure category to the lowest exposure category (Checkoway et al., 2015).[28] Because this change in methodology for exposure assessment blends the highly exposed people with the low and unexposed people and thereby induces bias toward the null reducing study sensitivity, these results were classified with* ***low*** *confidence.* [p. 1-443, lines 1-10]
>
> *Footnote 28, p. 1-443]: In Beane Freeman et al. (2009), for peak exposure there were four cases of ML who were unexposed, 14 cases with peak exposure from >0 to <2 ppm, 11 cases with peak exposure from 2 to <4 ppm, and 19 cases with peak exposure ≥4 ppm. In Checkoway et al. (2015), the new definition of peak exposure and the recategorization resulted in 27 cases of ML with peak exposures from 0 to <2 ppm, 11 cases with peak exposure from 2 to <4 ppm, and 10 cases with peak exposure ≥4 ppm. The Checkoway et al. (2015) results were classified with low confidence due to information bias and low sensitivity.*

As described in previous analyses of the NCI formaldehyde manufacturers and users cohort (Stewart et al. 2014, Hauptmann et al. 2004), there were no short-term industrial hygiene measurements to estimate peak exposures quantitatively. Accordingly, Beane Freeman et al. (2009) estimated peak exposure using a definition originally proposed by Stewart et al. (1986), who defined peak exposure as short-term exposures (generally less than 15 minutes) that exceeded job-specific 8-hour time-weighted average (TWA) exposure estimates. In the absence of actual short-term industrial hygiene measurements, Stewart et al. (1986) assigned peak exposure to jobs based on a review of routine and nonroutine tasks associated with a given job and in relation to the 8-hour TWA exposure. Furthermore, NCI investigators used the maximum peak exposure for workers who had job tasks with a presumed peak exposure. For workers assigned to jobs that did not have any presumed peak exposures based on job tasks, the NCI investigators substituted the highest TWA and called it the maximum peak exposure (Beane Freeman et al., 2009). This method of estimating peak exposure introduced exposure misclassification bias because workers who had a presumed short-term exposure (one that exceeded the TWA exposures based on work tasks) were mixed with workers who experienced a consistently continuous exposure (that is, did not have job tasks with short-term intermittent exposures).

In order to more accurately account for a time component that is inherently associated with a peak exposure (i.e. short-term exposures of approximately 15 minutes to one hour) that exceed the exposure averaged over 8 hours or more (that is, an 8-hr TWA), Checkoway et al. (2015) conducted additional analyses using a more conventional absolute peak metric (versus the relative peak used by Beane Freeman et al., 2011). Checkoway et al. (2015) defined peak exposures as those occurring in employment groups with at least one continuous month of employment in jobs identified in the original exposure assessment as likely exposing workers to short-term exposure excursions of $\geq$2 ppm to <4 ppm or $\geq$4 ppm on a weekly or daily basis. Checkoway et al. (2015) excluded workers who were only occasionally exposed to peaks (as infrequently as monthly) or who were exposed to short-term excursions occurring as frequently as hourly. In the former case, infrequent peaks are unlikely to have measurable impacts on cancer induction. In the latter case, excursions that occur on at least an hourly basis result in a higher TWA exposure overall. Such excursions occurring as frequently as hourly are more likely to reflect consistent high-level exposure rather than intermittent high-level exposure, and would be reflected in cumulative exposure estimates. The peak exposure metric applied by Checkoway et al. (2015) explicitly adds a time dimension that was missing from the analysis of peak exposure by Beane Freeman et al. (2009), in which exposures in workers with likely short-term excursions were mixed with the maximum TWA exposures for workers. We consider this a significant improvement over as well as a "sensitivity test" of the relative peak indicator generated by Beane Freeman et al. (2011).

EPA misinterpreted the impact of defining an absolute peak exposure metric on the study findings. When Checkoway et al. (2015) reclassified peak exposures as absolute rather than relative peaks, it did not shift "nine cases of myeloid leukemia from the highest exposure category to the lowest exposure category" as stated by the EPA. Instead, the reassignment of peak exposure resulted in four cases of myeloid leukemia in the category exposed to peaks >4 ppm in Beane Freeman et al. (2009) to the category exposed to peaks 2 to 4 ppm in the Checkoway et al. (2015). Another six cases of myeloid leukemia moved from the category with peaks >4 ppm to the category of 0 to 2 ppm peaks (which was the referent category in the Beane Freeman et al. 2009 analysis). Four cases of myeloid leukemia exposed to peaks 2 to 4 ppm in the Beane Freeman et al. (2009) analysis moved to the category of 0 to 2 ppm. One case of myeloid leukemia moved from lower category of peaks in the Beane Freeman (2009) analysis to a higher category of peaks >4 ppm) in the Checkoway et al. (2015) analysis. As a result, and applying a generous latency period, Checkoway et al. (2015) determined – based on the NCI exposure data – that only four (4) deaths due to AML occurred among workers associated with work areas and time periods in which absolute peak exposures likely occurred. Furthermore, and notwithstanding the small numbers of AML deaths occurring among groups of workers with peak exposures within reasonable latency periods, absolute peak is amenable to quantitative risk assessment, in contrast with relative peak exposure.

The EPA assigned low confidence to the exposure assessment in Checkoway et al. (2015) due to purported information bias and low sensitivity and suggested that the direction of expected bias would be toward the null, representing an underestimation of the actual risk. In fact, there is no such evidence of a bias toward the null in the reanalysis. Beane Freeman et al. (2009) reported a relative risk (RR) for myeloid leukemia of 1.78 (95% CI 0.87–3.64) for workers with peak

exposures ≥4 ppm. In the reanalysis of peak exposure, Checkoway et al. (2015) reported RRs for chronic myeloid leukemia of 3.07 (95% CI 0.83–11.40) and 5.32 (95% CI 0.81–34.90) for peak exposures ≥4 ppm for all workers and for workers employed one year or more, respectively. However, CML is a different malignancy and less plausibly related to environmental agents, whereas AML has been linked with high level exposures to benzene, smoking and chemotherapeutic agents. Checkoway et al. (2015) reported a p-value for trend of 0.07 for CML; however, there was no such association between peak exposure and AML in the Checkoway et al. (2015) reanalysis. There was no indication that the relative risk of AMLs increased with peak exposure (RR 1.71, 95% CI 0.72–4.07 and RR 1.43, 95% CI 0.56 – 3.63 for peak exposures ≥2.0–<4 ppm and ≥4 ppm, respectively, p-value for tend 0.31).

The EPA did not include (or even acknowledge) a highly relevant review (Checkoway et al. 2019) addressing the methodological uncertainties when relying on peak exposure as a surrogate of exposure for cancer risk assessment purposes.

We also published a comprehensive review of approaches to characterizing peak exposures and deriving cancer potency values from the epidemiological literature. Our analysis included nine epidemiological studies of environmental chemicals classified as carcinogens, including formaldehyde (Checkoway et al., 2019). This analysis provides additional valuable information that EPA should have considered and incorporated when evaluating the Checkoway et al. (2015) analyses conclusions to inform its approach to quantitative cancer potency characterization in the 2022 draft IRIS. Specifically, in addition to succinctly summarizing the results of the Checkoway et al. (2015) analysis, it also identifies issues with the characterization of peak exposure in in a case-control study of embalmers (Hauptmann et al. 2009). Furthermore, Checkoway et al. (2019) identified a pattern of limitations associated with using peak exposure data from epidemiological studies of seven additional substances (benzene, trichloroethylene, acrylonitrile, ethylene oxide, methylene chloride, styrene and/or butadiene) to inform risk characterization. Thus, the lack of a uniform approach is a critical issue that is not limited to formaldehyde. These methodological challenges include variability in peak exposure definitions across studies, lack of direct peak exposure measurements and reliance on expert judgement for exposure classifications, and potential exposure misclassification. The 2022 draft IRIS should have referred to this paper to better understand the limitations of the underlying formaldehyde epidemiological literature particularly with respect to the characterization of "peak" exposures to formaldehyde in some studies. Perhaps most importantly, the Checkoway et al. (2019) analysis substantiates the findings of Checkoway et al. (2015). The clear lack of an association with myeloid leukemia and its subtypes (AML and CML) in relation to cumulative exposure (the default exposure metric in epidemiologic studies based on its incorporation of both intensity and duration of exposure) do not support a causal association at any exposure level (Checkoway et al., 2015).